REMARKS

The Interview granted by the Examiner is much appreciated. The substance of the Interview is as stated by the Examiner in the "Interview Summary" document: proposed claim terminology changes were discussed in view of the cited prior art.

Claim 1 has been amended to simplify the prosecution and to address issues raised at the interview, for example, to clarify that it is the pharmaceutical composition itself which is substantially free of electrolytes; as noted by the Examiner, the carriers may typically contain some. Applicant's specification describes these electrolytes as "conventional additives" (page 6, last paragraph), such as found in the Mosby and Roblin PEG compositions. These are referred to in the art as "serum electrolytes" (see, e.g., Mosby), and that term is used here for clarity. The term "pharmaceutical" now modifies the "composition" of claim 1, to clarify the composition has medicinal properties, as opposed to the prior art bowel cleansers. The claim now is explicit that bowel cleansing is excluded. Also, the preamble to claim 1 has been rewritten to clarify that treatment of HE according to the invention includes the treatment of those both with and at risk of HE, to reduce and/or maintain plasma ammonia, as described e.g., page 4, lines 9 and 24, of the specification. Claim 4 has been rewritten as Claim 33. New claim 36 is reinstated original claim 11.

The Examiner newly rejects Claims 1, 4, 10, 19 and 20-25 under 35 USC §103(a) as unpatentable over Roblin *et al*. in view of Mosby (Mosby's Gen Rx, 8th edition, 1998), and further in view of Vicidomini *et al*. (EP '918), on the grounds that Roblin teaches treatment of hepatic encephalopathy during digestive hemorrhaging with 2L PEG by a Blakemore probe (nasogastric tube) and Mosby teaches the oral administration of PEG.

It is submitted that claims 1, 4, 10, 19, and 20-25 are not *prima facie* obvious over the references relied upon.

The Examiner cites *In re Kerkhoven* (205 USPQ 1069, CCPA 1980), for its ruling that, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the same purpose..." to support her rejection.

Roblin's purpose is to evacuate the intestinal blood resulting from digestive hemorrhage associated with HE by means of a PEG bowel lavage administered by nasogastric tubes.

Mosby (p. II-1770, cited by the Examiner) describes the use of a PEG lavage solution (Golytely® for bowel evacuation) either orally or via nasogastric tube prior to bowel examination.

Both Mosby and Roblin have a common purpose: bowel cleansing. In Mosby the purpose is to cleanse the bowel for examination. In Roblin the purpose is to cleanse the bowel of intestinal blood in hemorrhaging HE patients; this removes a large pool of proteins from the digestive tract, where it would otherwise be metabolized by intestinal flora, releasing toxic amounts of NH_3 in the process. Consequentially, ammonemia (high blood levels of ammonia) is alleviated in the Roblin process. The Examiner repeats that the controlling issue is the broad purpose of Applicant's inventions and Roblin's procedures; i.e., to treat HE. In fact, the controlling issue is the method by which this is done. Applicant's method steps are patentably distinct from those of the prior art.

The Examiner contends that it would be obvious to substitute the orally administered PEG bowel lavage of Mosby for the nasogastric tube lavage in the method of Roblin, motivated by ease of administration. However, Roblin's protocol is limited to the treatment of very sick patients in abnormal states of consciousness ("Administration of 2L of [PEG]... allowed the return of consciousness in two hours."), making this substitution impossible. Even if such a substitution were *arguendo* to be considered obvious, this still would not provide Applicant's

methods of claim 1 and claims dependent thereupon, which are not intended to and do not cleanse the bowel.

The Examiner further relies on Kerkoven to support the contention that it would be "obvious to the skilled artisan to combine PEG (Roblin) and lactulose (Vicidomini) motivated by their having been taught by the prior art to be useful in treating hepatic encephalopathy...", and that it would be obvious to make this formulation for oral administration as it is taught by Mosby to administer PEG orally.

To the contrary, Mosby specifically warns against adding any other ingredient to the described GoLytely® PEG/electrolyte bowel cleansing solution ("WARNINGS," p. II-1769). The Fortrans® bowel cleansing solution used by Roblin is also a PEG/electrolyte solution, more or less equivalent to GoLytely®. One skilled in the art would thus not consider adding anything at all to either Mosby's or Roblin's PEG solution, including lactulose.

Further, there is absolutely no reason for one skilled in the art to contemplate such a combination. As discussed *infra*, lactulose must be retained in the bowel to effectively reduce free ammonia present there. It would be completely superfluous in a bowel lavage such as Roblin's, which is designed to completely empty the digestive tract as fast as possible, on an emergency basis.

Additionally, the Kerkoven decision was directed to non-pharmaceutical compositions containing ingredients with predictable properties and results, unlike pharmaceuticals. Rarely, if ever, will a combination of say, two detergents, fail to clean, to one extent or another. Rarely, if ever, will they interact with each other to cause unexpected results, such as failing to clean at all.

Pharmaceuticals are well-recognized in the art as unpredictable. A combination of pharmaceuticals, each of which can be used to treat a condition or a disease, can be devastating in their results if combined. Also, they can work against each other

in combination, rendering the effectiveness of each singly useless in combination.

For these reasons, this rejection of the enumerated claims for *prima facie* obviousness cannot be sustained.

Additionally, even if it were to be assumed *arguendo* that *prima facie* obviousness can be found, unexpected results from the claimed methods and compositions are disclosed. As discussed in the specification, PEG is a known osmotic laxative. PEG attracts fluids into the GI tract, and increases intestinal mobility, thereby accelerating the movement of intestinal contents through the system. Lactulose is a mild osmotic, but is used for treating HE primarily because it reduces the accumulation of free NH_3 from protein digestion in the gut by interaction with intestinal flora, as described in detail in the specification. In order to do so, it must be retained in the digestive system for a sufficient period of time to convert the free ammonia to harmless derivatives. Thus, adding a laxative such as PEG to lactulose is counterintuitive. One skilled in the art would expect this merely to accelerate the removal of lactulose from the gut before it is able to serve its purpose, thereby rendering it as useless as it would be if combined with Robin's bowel lavage.

As discussed in the specification, lactulose, the current treatment of choice for HE, has a very bad taste, as well as unpleasant side effects such as bloating, nausea, and cramping, and patient compliance with typical regimens of lactulose *per se* are not good. The consequences of this non-compliance are life-threatening. Applicant provides an improved method for treating hyperammonemia associated with HE using a combination of PEG and lactulose, wherein the amount of lactulose needed for effective free NH_3 reduction can be reduced, while maintaining effectiveness of the treatment. [This may be due in part to the enhancement of the mild osmotic properties of lactulose by the stronger osmotic properties of PEG which may draw more free NH_3 into the intestine for conversion and/or elimination.] Importantly, the combination

of PEG and lactulose provides an effective composition far more palatable than lactulose alone, thus significantly increasing patient compliance, especially in long term maintenance dosage regimens.

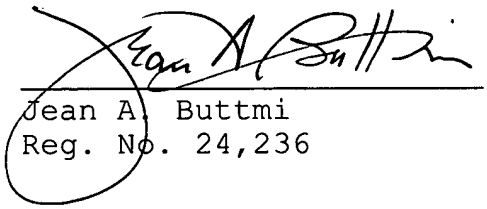
It is accordingly submitted that these results could not have been expected, and that any presumption of *prima facie* obviousness has been rebutted. Reconsideration and withdrawal of this rejection is therefore solicited.

The Examiner further rejects Claims 1-32 under 35 USC §103(a) over Roblin *et al.*, Mosby and Vicidomini *et al.*, as applied in the preceding rejection, and further in view of Pelham. The Examiner is referred to Applicant's discussion of Roblin *et al.*, Mosby, and Vicidomini, *supra*.

The Examiner states that the Pelham reference teaches that "lactulose is a poorly absorbed disaccharide (i.e., fiber)". In fact, Pelham defines lactulose as a poorly absorbed disaccharide. The Examiner wrongly equates a disaccharide to a fiber. As discussed at length in Applicant's amendment of 1 November 2005, disaccharides are sugars - crystalline and water-soluble; see, e.g., http://en.wikipedia.org/wiki/Disaccharide, printed 3/16/06, copy enclosed. Further, Pelham defines fiber [0027] as polysaccharides (not disaccharides) or lignins resistant to hydrolysis by human digestive enzymes.

This rejection relies on a misinterpretation of Pelham *et al.* and a factual error which Applicant has rebutted. Reconsideration and withdrawal is accordingly respectfully requested.

Respectfully submitted,



Jean A. Buttmi
Reg. No. 24,236

April 24, 2006

HOFFMAN, WASSON & GITLER, PC
2461 South Clark Street
Suite 522
Arlington, VA 22202
703.415.0100

Customer No. 20741

Attorney's Docket: A-8636.ROA/cat